transduces human target cells with higher transduction efficiencies in neuronal cells than in non-neuronal cells.--

REMARKS

Reconsideration is requested.

Claims 1-20 have been canceled, without prejudice. Claims 21-39have bee added. Support for the amendments may be found throughout the specification.

The specification has been amended to include a reference to the prior applications, as suggested by the Examiner on page 2 of he Office Action dated July 8, 2002 (Paper No. 7), however the Examiner is urged to appreciate that the present application, which is a 371 application based on a PCT application filed on 21 May 1999, is, for all purposes except 35 U.S.C. § 102(e) an application filed prior to November 29, 2000. See, 35 U.S.C. § 363. Accordingly, the procedure described by the Examiner requiring a petition and surcharge and statement are not believed to be required however the Examiner is requested to advise the undersigned if otherwise. In the event anything further is required in this regard, the Examiner is further requested to provide a basis in the law, rules and/or MPEP for such a requirement for 371 application with an international filing date prior to November 29, 2000.

Return of an initialled copy of the PTO 1449 Form filed November 22, 2000, pursuant to MPEP § 609, is requested. While page 1 of the Office Action dated July 8, 2002, indicates that a PTO 1449 Form was attached to he Office Action, none was received by the undersigned with the Office Action.

Claim 1 has been rewritten as new clam 20 further define "selectively transducing a target site" by incorporation of the feature that the system is capable of selectively

transducing human target cells with higher transduction efficiencies in neuronal cells than in non-neuronal cells. Basis for this recitation can be found from original claim 8 and the description on page 38, lines 9-16 and page 40, lines 9-11.

The Examiner is urged to appreciate that presently claimed invention, such as recited in claim 20, relates to retroviruses pseudotyped with the rabies G protein which selectively transduce neuronal cells with higher transduction efficiencies than non-neuronal cells.

The claims have also been rewritten to obviate the Section 112, second paragraph rejection of claims 1-16 and 20 noted on pages 9-11 of Paper No. 7. The pending claims are submitted to be definite.

The Section 112, first paragraph, rejection of claim 12 is moot in view of the above. Claim 12 has been rewritten as new claim 30, which is submitted to be supported by an enabling disclosure. Consideration of the following in this regard is requested.

Claim 30 relates to a pharmaceutical composition comprising a retroviral delivery system as defined in claim 21 and a pharmaceutically acceptable diluent. Neither claim 30, nor canceled claim 12, require that the claimed composition be use in gene therapy, as the Examiner apparently believed of claim 12. The basis of the Examiner's rejection of claim 12 appeared to be an assertion that the field of gene therapy is unpredictable. However, the applicants believe that the Examiner has overlooked that canceled claim 12 and pending claim 30 relate to a pharmaceutical composition comprising the retroviral delivery system of claim 21 and does not relate to a method of gene therapy as such.

More importantly, the presently claimed invention is sufficiently exemplified to enable a person of ordinary skill in the art to make and use the claimed invention. The specification provides extensive guidance on the preparation of the delivery system of the invention together with evidence of its ability to transduce neuronal cells selectively. Furthermore, the production of pharmaceutical compositions using pharmaceutical adjuvants, diluents and excipients etc is well known in the art and, moreover, is described in the specification (see, for example, pages 24-25).

The claims are submitted to be supported by an enabling disclosure.

The Section 102 rejection of claims 1-4, 6-11 and 13-20 over Bremel *et al* (US 6,080,912) is moot in view of the above. The claims are submitted to be patentable over Bremel *et al* and consideration of the following in this regard is requested.

Bremel *et al* describes a method for introducing genes into a pre-fertilisation oocyte in order to enable the generation of a transgenic animal. Specifically, Bremel *et al* provide a method for the generation of transgenic animals in which the transgene is incorporated into the genome of <u>all</u> cells of the embryo and resultant organism, thus avoiding the generation of transgenic organisms which are "mosaic for the presence transgene" (see, for example, abstract, col 10 lines 6-10 and col 24 lines 7-11).

In contrast, the presently claimed invention provides a retroviral delivery system which may be used in the <u>selective transduction</u> of a target site. In particular, the retroviral delivery system of the presently claimed invention selectively transduces human target cells with higher transduction efficiencies in neuronal cells than in non-neuronal cells and thus may be useful in, for example, gene therapy applications, for example in the targeting of brain cells etc. As the retroviruses described by Bremel *et al*

are adapted for use in a method in which oocytes are transduced such that all cells of the resulting organism comprise the transgene, Bremel does not teach retroviruses which are capable of selectively transducing target cells with higher transduction efficiencies in neuronal cells than in non-neuronal cells i.e. such that only selected cells of an organism comprise the transgene.

Indeed, if anything, Bremel *et al* teaches away from the presently claimed invention in that the retroviruses required for the method described by Bremel *et al* are required for transduction of oocytes such that all cells of the resulting organism comprise the transgene.

The claims are submitted to be patentable over Bremel *et al*.

The Section 103 rejection of claim 5 over Bremel *et al* (US 6,080,912) in view of Olsen (US 6,277,633), is moot in view of the above. The pending claims are submitted to be patentable over the cited art and consideration of the following in this regard is requested.

As will be recognised from the above, the relevant claim requires that the retroviral delivery system is pseudotyped with the rabies G protein and is capable of selectively transducing neuronal cells with higher transduction efficiencies than non-neuronal cells. As described above, Bremel *et al* neither teaches nor suggests retroviral delivery systems capable of selectively transducing neuronal cells with higher transduction efficiencies than non-neuronal cells and, indeed, arguably teaches away from such retroviral delivery systems.

Olsen merely describes an EIAV vector pseudotyped with a VSV-G protein. There is no teaching or suggestion in the cited art that rabies G protein may be used to

produce an EIAV vector which transduces neuronal cells with higher transduction efficiencies than non-neuronal cells. Indeed, the only protein suggested for pseudotyping is the VSV-G protein, which, as described in col 9, lines 7 to 12 of Olsen, confers a very broad host range.

Neither Bremel nor Olsen, individually or combined, suggest that retroviral delivery systems as presently claimed can be provided in which the EIAV vector (or any other retrovirus) transduces neuronal cells with higher transduction efficiencies than non-neuronal cells. Moreover, Bremel provided no motivation whatsoever to the ordinarily skilled artisan to replace the VSV-G protein of Olsen with the rabies G protein, let alone providing any indication of selectivity of transduction. Indeed, Bremel *et al* teach that VSV-G is chosen for use therein because of its extremely broad host range (col 9 lines 52 - 54) and suggests that the Rabies G protein has a high degree of conservation (with respect to amino acid and functional conservation), thus implying that the replacement of VSV-G with Rabies G protein would not alter the broad host range and thus the transduction selectivity of a vector.

The claims are submitted to be patentable over the cited art.

The Section 101 rejection of claim 11 is moot. Claim 11 has been rewritten as new claim 29, which is submitted to define patentable subject matter.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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